

Do Proton Pump Inhibitors Reduce the Incidence of Pharyngocutaneous Fistulae following Total Laryngectomy?

by

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LIST OF ABBREVIATIONS

<i>GORD/GERD</i>	Gastroesophageal reflux disease
<i>LPR</i>	Laryngopharyngeal reflux
<i>GPR</i>	Gastropharyngeal reflux
<i>PCF</i>	Pharyngocutaneous fistula
<i>PPI</i>	Proton pump inhibitor
<i>TOF</i>	Tracheoesophageal fistula

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ABSTRACT

DO PROTON PUMP INHIBITORS REDUCE THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULAE FOLLOWING TOTAL LARYNGECTOMY?

BACKGROUND:

Pharyngocutaneous fistula is a common complication of total laryngectomy. We hypothesised that perioperative proton pump inhibitor (PPI) treatment could reduce the incidence of pharyngocutaneous fistulae.

METHODS:

This prospective placebo-controlled double-blind randomised controlled trial compared PPI treatment (14 days enteral omeprazole) with a placebo in patients undergoing primary total laryngectomy. The incidence of pharyngocutaneous fistula was recorded.

RESULTS:

Forty patients were randomised into PPI (N = 21) and placebo arms (N = 19). One of 21 patients receiving omeprazole developed a fistula in comparison to 6 of 19 placebo group patients ($p=0.04$). No other statistically significant risk factors for pharyngocutaneous fistula were identified. The mean hospital stay of patients with and without a fistula was 32 and 7.5 days respectively.

CONCLUSIONS:

PPI prophylaxis was associated with a statistically significant reduction in pharyngocutaneous fistulae. As fistulae are associated with prolonged hospitalisation and morbidity, PPIs are recommended for patients undergoing total laryngectomy.

Keywords: pharyngocutaneous, fistula, laryngectomy, reflux, proton pump inhibitors, omeprazole.

PART A: PROTOCOL

DO PROTON PUMP INHIBITORS REDUCE THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULAE FOLLOWING TOTAL LARYNGECTOMY?

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BACKGROUND

Pharyngocutaneous fistula (PCF) is a common complication following total laryngectomy and is a cause of significant patient morbidity. The reported incidence of PCF ranges from 3 to 65%; with a reported average of 17.4%;¹ the incidence at our centre has been previously evaluated and found to range between 15.4% and 20%.² Spontaneous closure of PCF generally occurs. However surgical closure may be required, either by direct closure of the pharyngeal mucosa or by use of a tissue flap. It has been demonstrated that development of PCF has been found to be associated with a significantly increased duration of hospital stay. Fatal bronchopneumonia, mediastinitis and severe sepsis, in addition to death as a result of erosion of the carotid artery by a PCF have also been described.

Numerous studies have examined the likely aetiology of PCF post-total laryngectomy; multiple risk factors have been thus far identified.³⁻⁸ Risk factors may be categorised into patient, disease and procedure-related factors, summarised below.

<i>Patient-related</i>	<i>Disease / Management-related</i>
Co-morbid illness: CCF Diabetes Liver disease	Prior tracheostomy
Low post-operative albumin	Concurrent neck dissection
Low post-operative haemoglobin / Peri-operative blood transfusion	Previous radiotherapy
Post-operative vomiting	Pharyngolaryngectomy
	Pharyngeal myotomy
	Positive surgical margins
	Presence of lymph node metastases

Patients with HIV have been found to be at increased risk of developing squamous cell carcinoma of the larynx; the disease is also known to follow a more aggressive course with increased treatment-related morbidity.⁹ The influence of HIV status on the incidence of PCF has not been published.

Gastro-oesophageal reflux disease (GORD) is also increasingly recognised as a potential aetiological factor for malignancy of the upper aero-digestive tract, including the larynx. It has been estimated that the single greatest risk factor for squamous cell carcinoma (SCC) of the larynx is cigarette smoking. Alcohol consumption (in isolation) is also associated with an increased risk. Smoking and alcohol consumption are also major risk factors for GORD.¹⁰ A high incidence of GORD and GPR (gastropharyngeal reflux) has been detected in patients with SCC of the larynx in both the pre- and post-laryngectomy population.¹¹⁻¹³

Not only is it suspected that reflux may play a role in the aetiology of squamous cell cancer of the larynx but also that it may contribute to complications in head and neck cancer patients after surgery or during radiotherapy. Qadeer et al found that acid suppression therapy post-laryngectomy may have protective effect on laryngeal cancer recurrence.¹⁴

As a class, proton pump inhibitors (PPIs), such as omeprazole and lansoprazole, are the most potent suppressors of acid secretion. They act by irreversibly binding to and inhibiting the H^+, K^+ -ATPase enzyme of the gastric parietal cell. PPIs may be administered intravenously, orally and via a naso-gastric feeding tube.

Antacid medications are employed by some surgeons in the post-operative period following total laryngectomy with the aim of reducing the incidence of post-operative pharyngocutaneous fistulae. To date, medical literature describes the use of H_2 antagonists (such as cimetidine and ranitidine) as antacids. Seikaly and Park reported a significant decrease in the incidence of PCF with a post-operative regimen of intravenous ranitidine and metocloperamide hydrochloride (a prokinetic);¹⁵ Twenty-three prospective cases were treated with the antacid regime (PCF incidence 0%), in

comparison to 17 retrospective controls that did not receive antacid treatment (PCF incidence 26%). A significant reduction in PCF incidence was also described by Sarria Echegaray et al in 2000 following the addition of a prokinetic medication to their post-operative regime.¹⁶

To the knowledge of the investigators, neither the use of PPIs, nor the use of an enteral antacid preparation, has been examined; an exciting potential application of the PPI as gastro-oesophageal reflux prophylaxis exists in the post-total laryngectomy setting.

PURPOSE OF THE STUDY

The primary aim of the study is to determine whether administration of a PPI in the immediate postoperative period reduces the incidence of pharyngocutaneous fistula in patients who have undergone total laryngectomy. Our hypothesis is that PPIs reduce the incidence of PCF post-laryngectomy.

METHODOLOGY

STUDY DESIGN

A prospective randomised controlled trial; it will be a placebo-controlled, double blind study (materials permitting).

A PPI, 20mg omeprazole, will be administered once daily for 14 consecutive days. The first dose will be given the day before total laryngectomy. Initial post-operative administration will be via the naso-gastric (NG) feeding tube and then per os when the patient is feeding orally. The MUPS preparation of omeprazole is suitable for use via an NG tube. An oral preparation of omeprazole may otherwise be used when the patient is not dependent on NG feeding. Both preparations are stocked by the Groote Schuur Hospital pharmacy. It is the investigators' wish that widely available and therefore clinically applicable preparations be used.

It is appropriate that existing prescribing guidelines, of both the manufacturers of the medication and of local pharmacology authorities (including the South African Medicines Formulary¹⁷) are followed.

Recommended dosage is 20mg once daily for treatment of both gastric and duodenal ulcers, reflux oesophagitis, NSAID-associated gastroduodenal lesions, symptomatic gastro-oesophageal reflux disease and functional dyspepsia, in addition to the prophylaxis of NSAID-associated gastroduodenal lesions.

Within communications with possible manufacturers of the placebo drug, it has been and will continue to be stressed by the investigators that the placebo and associated paraphernalia must be identical to that of the active drug. The tablet or capsule must be of identical size, shape, colour, and weight. A placebo for the MUPS preparation which is to be dispersed in water must also have similar dispersing properties and appearance when dispersed. Furthermore the packaging and labelling of the placebo must also be identical, when viewed by the patient, nursing and medical staff. When the placebos are received from the manufacturer, it is intended that this will be verified by pharmacy staff.

Following Health Sciences Faculty Human Research Ethics Committee (HSF HREC) approval, the study will be formally discussed with the Manager of the Inpatient Pharmacy of Groote Schuur Hospital, Mr. V. Naicker. Pharmacy expertise will be sought and appreciated; jointly agreed procedures related to the study will be established and documented in writing. It is intended that a specific, named pharmacist(s), holding Good Clinical Practice certification, be allocated to the study. This pharmacist(s) would be responsible for allocation of the grouping nomenclature, supervision of storing and dispensing of materials, in addition to acting as a liaison between pharmacy and the investigators. All materials related to the study (including both the active drug and placebo) will be stored in a separate, clearly labelled area within the inpatient pharmacy prior to dispensing. It is intended that both the active drug and placebos be dispensed by the F8 ward nursing staff in the standard manner along with any other medications the patients may be receiving. Specific information sessions regarding the study, both prior to the start of the study and at regular intervals within the study, will be conducted with the ward staff that will be sending the patient medication charts to the Inpatient Pharmacy and dispensing medications.

In order to conceal the identity of the drug and the placebo, patients will be randomised into one of two treatment groups. The assignment of the active drug and the placebo will be made by and known only to allocated pharmacy staff. Accordingly, nursing staff of the ENT ward (F8), medical staff within the ENT department including the investigators of the study will be unaware of the grouping. Only upon formal closure of the trial will the true identity of the two groups be revealed to the investigators.

This grouping will be reflected by a special sticker label placed on the patient's hospital folder and also on the patient's inpatient medication chart. In addition to stating the grouping of the patient, this sticker will detail the patient hospital number, the name of the trial, the names and contact details for the investigators, and names and contact details of allocated pharmacist(s). The sticker labels will be of a bright colour in order to facilitate recognition.

Accordingly, when a request for dispensing of medication is made to inpatient pharmacy by means of the medication chart, the 14-day course may be dispensed. This course will be started on the day immediately preceding the day of the total laryngectomy surgery and be continued for 14 consecutive days. The treatment will therefore will be taken initially as an inpatient and either completed within the inpatient stay (if the inpatient stay is greater than 13 post-operative days), or completed at home (if the patient is discharged before the 13th post-operative day).

Patients will be randomised shortly before total laryngectomy. The total laryngectomy surgery and the postoperative care will remain unchanged other than the addition of the PPI. The surgical method of closure of pharynx will be standardised: 2 layer closure with a vicryl suture, with the least wound tension (either a horizontal or T-shaped suture line), performed either by a consultant or by a trainee under consultant supervision.

The principal outcome of the study is the development (or lack of development) of a pharyngocutaneous fistula (PCF); this objective outcome usually occurs within 10 days of surgery. Existing departmental procedure will continue to be followed; wounds are reviewed by an ENT Registrar

and/or Consultant on a daily basis whilst the patient is an inpatient and subsequently at each outpatient encounter thereafter within the LE32 Radio-Oncology clinic framework.

A possible PCF will be detected clinically, as evidenced by wound breakdown, erythema, and/or leakage of serous, sanguinous or purulent fluid from a wound or the surrounding skin.

Upon clinical suspicion of a PCF, every patient will undergo a radio-opaque contrast swallow at Groote Schuur Hospital. This is consistent with existing departmental practice. Radiological confirmation of the presence of a PCF in these cases will serve as an objective outcome measure.

All patients will be followed within the existing follow-up framework of the LE32 Head and Neck cancer clinic.

CHARACTERISTICS OF THE STUDY POPULATION

All patients at Groote Schuur hospital undergoing total laryngectomy for squamous cell carcinoma of the larynx are potential participants. Due to the nature of the study population, it is not expected that vulnerable patients will be among the patients enrolled (e.g. minors, terminally ill).

We are planning a study of two independent groups; one group will be treated with a PPI (case group) and the second group will not receive the treatment (control group) with 1 treated per untreated case. It is intended that the control group receive a placebo and that patients, nursing staff and clinicians are blinded to the patient's group.

Historical data from the department indicates that the 'failure rate' (rate of PCF) among controls is 0.2.² If the true 'failure rate' for case subjects is 0.0, we will need to study 44 experimental subjects and 44 control subjects to be able to reject the null hypothesis that the 'failure rates' for case and control subjects are equal with probability (power) 0.8. If the true 'failure rate' for case subjects is 0.01, 50 case and 50 control subjects will be needed. The Type I error probability associated with this test of this null hypothesis is 0.05

Using an alternative scenario, predicting a decrease in incidence from 0.2 (20%) to 0.05 (5%), 88 patients would be required in each arm.

It is therefore projected that our intended initial sample size will be 50 patients in each arm of the study. It is recognised that this reflects a marked reduction in the incidence of PCF. Existing literature related to this study has however described a significant decrease in the incidence of PCF using a post-operative anti-acid regime; Seikaly and Park reported a decrease in incidence from 26% (controls; no antacids given) to 0% (cases; intravenous ranitidine and metocloperamide given).¹⁸ Furthermore, in terms efficacy of acid suppression, omeprazole has demonstrated therapeutic results superior to any other previous medical treatment.¹⁹

RECRUITMENT AND ENROLMENT

Patients will be enrolled prior to total laryngectomy surgery either in an outpatient clinic or ENT ward setting, after consent for surgery has been obtained. Patients will be enrolled by an ENT registrar or consultant. The study will not be advertised.

According to the South African Medicines Formulary (8th edition), omeprazole is contraindicated in patients with cancer of the stomach and use is cautioned in patients with porphyria and severe liver disease. It is not anticipated that patients with the aforementioned problems will be within the study population; however those conditions would also be considered as exclusion criteria. Patients with a known allergy to omeprazole will be excluded from the study along with those patients who do not consent to study inclusion

RESEARCH PROCEDURES AND DATA COLLECTION METHODS

Data will be recorded in relation to patient history, the characteristics of their disease and the operative management (detailed in Appendix I); this will be done by either the primary investigators or a registrar within the ENT department. Care will be taken to ensure all potential confounding factors

will be recorded so that these may be taken into account during data analysis.

Method of randomisation: Computer generated, on the basis of random permutation blocks within strata with multiple stratification variables, so that known risk factors for PCF may be taken into consideration during randomisation.

Post-operatively, the standard existing management will be followed for post-operative care. This includes an antibiotic regime of a single dose of intravenous Kefzol given intraoperatively followed by 24 hours of intravenous antibiotics (Ampicillin 1g tds and Metronidazole 500mg tds). Post-operative feeding will be determined by the existing departmental Early Feeding Protocol (Appendix II).

DATA SAFETY AND MONITORING

The primary investigator will act as study co-ordinator and will be responsible for the safety of the collected data. It is anticipated that interim analyses will be made (e.g. at 4-month intervals). Should a highly significant outcome be obtained earlier than projected, early closure of the study may be considered in order for change of practice and dissemination of findings.

DATA ANALYSIS

Statistical data analysis will be performed. We anticipate that a continuity-corrected chi-squared statistic or Fisher's exact test will be used to evaluate our hypothesis.

RESULTS / OUTCOME MEASURES

The incidence of pharyngocutaneous fistula will be compared between the two groups of patients. Patient demographics and other factors known to affect fistula rate will be recorded, and will be included in randomisation, where possible. Duration of post-operative hospital stay (until patient is fit for discharge from a surgical perspective) will also be recorded.

PROJECTED COSTS

The cost of the omeprazole and placebos are the only projected costs. Current Groote Schuur pharmacy costing (state tender) for a 20mg MUPS preparation (AstraZeneca; MCC registration number 34/11.4.3/0223) estimates the cost per patient to be R273.75 for a 14 day course; a 20mg non-MUPS preparation (Dr.Reddy; MCC registration number 34/11.4.3/0300) would cost R7.35 for a 14 day course. The cost of medication may be offset by reduced costs in terms of both hospital stay and operating theatre use if the PPI is proven to reduce the incidence of PCF.

Following ethics committee approval, an application to the South African Society of Otorhinolaryngology Head and Neck Surgery will be made for a research grant in order to cover these costs. It is anticipated that the MUPS preparation and equivalent placebos will need to be purchased for the study; Dr. Reddy pharmaceuticals has given an initial indication that they will donate the non-MUPS preparation and equivalent placebos.

RISKS TO PATIENT

The only alteration to patient care and therefore source of possible risk will be the addition of the PPI medication, received by half of the study population. PPIs have been extensively clinically tested and are widely used. Much of the side effects and concerns regarding omeprazole relate to administration in severely ill patients and to long term administration; the setting of this study encompasses neither of these special situations.

Due to the nature of the total laryngectomy surgery and the associated necessary post-operative care, it is reasonable to estimate that patients within the study will be inpatients for a minimum of the first 5 days of the 14 day-treatment course. Patients receiving the active drug will therefore be monitored closely; possible side-effects are likely to be promptly identified and managed appropriately.

POTENTIAL BENEFITS

Patients in the PPI arm of the study may benefit, should PPIs be shown to be effective. A decreased incidence of PCF may be associated with less morbidity and mortality post-total laryngectomy, in addition to reduced hospital stay. The study will also advance the local scientific knowledge and refine patient care. It is hoped that publication of the research will also benefit national and international centres, facilitating an evidence-based approach to post-operative care of the laryngectomee.

ALTERNATIVES TO PARTICIPATION

Should a patient choose not to participate in the study, the patient will be cared for without prejudice or deviation from established departmental care. Surgery for cancer of the larynx is performed in several public hospital settings within South Africa in addition to the private sector.

INFORMED CONSENT PROCESS

Consent will be obtained in writing prior to total laryngectomy, either by the Primary Investigator or a specifically trained and instructed member of the ENT department (see Appendix I). The patient will be deemed to be competent to consent to inclusion in the study if he/she has been deemed competent to consent for total laryngectomy. If the patient is not able to understand the language of the consent form, a translator who is unaffiliated to the study will be employed, and counter-signature given. The study population will not include minors; a consent form suitable for adults has been prepared.

It is existing departmental policy that all patients with cancer of the larynx due to undergo total laryngectomy surgery are offered HIV testing and appropriately counselled; this practice will not be amended.

PRIVACY AND CONFIDENTIALITY

The primary investigator will act as study co-ordinator and will be responsible for the safety of the collected data. Data collected and recorded on data sheets will be computerised. All materials will be kept in a locked room within the ENT ward. Hospital number will be recorded as a patient identifier within the raw data in order to permit verification of information at later stages during analysis, if needed. Patient-specific information will neither be required nor included during data analysis.

REIMBURSEMENT FOR PARTICIPATION

It is not expected that participants will incur any extra personal costs in terms of transport, time or healthcare costs. Patients will not be given an incentive, monetary or of any other kind, in return for study participation.

EMERGENCY CARE AND INSURANCE FOR RESEARCH-RELATED INJURIES

A need for emergency care and/or insurance is not anticipated.

WHAT HAPPENS AT THE END OF THE STUDY?

Should the hypothesis be statistically proven, and the medication shown to be efficacious and practically applicable in this setting, it is hoped and anticipated that a post-laryngectomy PPI be given to all patients in future.

The investigators plan to submit findings of the study to an international scientific journal for publication.

No proprietary interests to declare.

No investigator will receive incentives for recruiting participants to the study.

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PART B: STRUCTURED LITERATURE REVIEW

DO PROTON PUMP INHIBITORS REDUCE THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULAE FOLLOWING TOTAL LARYNGECTOMY?

Introduction

Total laryngectomy is the mainstay of treatment for advanced laryngeal cancer and has been performed for over 150 years since Billroth's first description in the 1870s. This surgical removal of the entire larynx results in an anterior hypopharyngeal defect that is typically closed by suturing. The resultant suture line is of considerable length; in the range of 8-10cm. Meticulous approximation of this thin and delicate tissue is required to achieve closure of the defect and increase the likelihood of healing. Several centres have employed an alternative method of closure using a mechanical linear stapling device since its initial description in 1990;¹ this is not used in our setting, where approximately 30 such surgeries are performed each year. In addition to careful surgical technique, current local perioperative practice includes 24 hours of intravenous antibiotics and use of an 'early feeding' protocol (Appendix III). Antacid treatments are not currently routinely given.

Pharyngocutaneous fistula (PCF) is a common complication following total laryngectomy surgery and is a cause of significant patient morbidity. This salivary leak that communicates between the pharynx and the skin is associated with wound breakdown and typically occurs at the level of the surgical incision or less commonly in the region of the tracheal stoma.² The reported incidence of PCF ranges from 3% to 65% with a reported average of 17.4%;³ the incidence at our centre has been previously evaluated and found to range between 15.4% and 20%.⁴ Spontaneous closure of a PCF generally occurs; however surgical closure may be required, either by direct closure of the pharyngeal mucosa or by use of a tissue flap. Development of a PCF delays oral feeding and is associated with a significantly increased duration of hospital stay. At our institution the median inpatient stay was

found to be 10.5 days for patients without PCF compared to 26 days for PCF cases.⁴ This significant increase in hospital stay is mirrored in similar literature. Fatal bronchopneumonia, mediastinitis and severe sepsis, in addition to death as a result of erosion of the carotid artery by a PCF have also been described.^{5–7} It is the principal short-term post-surgical complication to be avoided; all potential risk factors must therefore be minimised.

Objectives and Search Strategy

The objective of the literature review is firstly to review the existing evidence relating to the aetiology of PCF post-total laryngectomy and more specifically the role of gastroesophageal reflux in the laryngectomy patient. Existing levels of evidence and research methods employed will also be examined. Deficiencies in current published knowledge and scope for further research will be identified.

A systematic search for relevant literature was conducted using Medline® and PubMed® systems. The following key words were used: reflux, laryngectomy, pharyngocutaneous fistula, salivary leak, larynx, cancer, prophylaxis, proton pump inhibitor. No relevant review was found in the Cochrane database.

Aetiology of Pharyngocutaneous Fistula

Numerous studies have examined the likely aetiology of PCF post-total laryngectomy. The meta-analysis of Paydarfar and colleagues³ published in 2000 identified 65 studies relating to risk factors contributing to PCF formation, whilst the published literature extends over a period of 40 years.^{8,9} Multiple risk factors have been thus far identified.^{10–14} Risk factors may be categorised into patient, disease and management-related factors, summarised below (Table 1). Preoperative radiotherapy is currently thought to be the most significant factor thus far identified.^{15,16}

Patient-related	Disease / Management-related
Co-morbid illness: congestive cardiac failure, diabetes, liver disease	Prior tracheostomy
Low postoperative haemoglobin / Peri-operative blood transfusion	Concurrent neck dissection / Extension of surgery to the pharynx
Postoperative vomiting	Previous radiotherapy
Low postoperative albumin	Pharyngeal myotomy
	Positive surgical margins / Presence of lymph node metastases
	Method of pharyngeal closure
	Use of peri-operative antibiotics

Table 1: Proposed risk factors for development of pharyngocutaneous fistula following total laryngectomy

Retrospective cohort studies form the majority of the basis of this evidence. One of the largest cohorts was evaluated by White et al, evaluating a total of 259 laryngectomy patients (Oxford Centre for Evidence Based Medicine Level of evidence 2B¹⁷).¹⁵ This was, however, a heterogeneous group of 113 primary laryngectomies with the remainder comprised of 'salvage laryngectomies' (performed after failure of other primary treatment such as partial surgery, radiotherapy and chemoradiotherapy) and extended laryngectomies combined with pharyngectomy or glossectomy and with use of a variety of free flaps. Two particular variables were associated with an increased risk of PCF; prior radiotherapy (P=0.03) and hypothyroidism (P<0.0002). Study method relating to postoperative feeding and antibiotic protocol was not described.

Author	Total no. (fistula rate)	Factors described
Aprigliano ¹⁸ , 1990	625 (9.1%)	RT, NG tube use,
Bresson et al ¹⁹ , 1974	148 (65.5%)	RT, stage
Cavalot et al ¹⁶ , 2000	293 (10.9%)	RT , Hb, systemic disease
Chee & Siow ²⁰ , 1999	69 (15.9%)	RT, positive margins
Cummings et al ²¹ , 1977	155 (16.1%)	RT
Fradis et al ²² , 1995	56 (12.5%)	RT, ND, stage, RT + ND
Gall et al ²³ , 1977	233 (4.3%)	RT, site
Hier et al ²⁴ , 1993	126 (19.0%)	RT, blood transfusion, stage
Horgan & Dedo ²⁵ , 1979	135 (14.8%)	RT, antibiotics, ND, PT, systemic disease
Ikiz et al ²⁶ , 2000	92 (8.7%)	RT, Blood transfusion , stage, PT
Johansen et al ²⁷ , 1988	106 (32.1%)	RT, antibiotics (metronidazole), site
Joseph & Shumrick ²⁸ , 1973	23 (34.8%)	RT, RT + ND
Kent et al ²⁹ , 1985	66 (7.6%)	RT, ND, systemic disease, site, stage
Krouse & Metson ³⁰ , 1992	109 (4.6%)	RT, systemic disease
Lavelle & Maw ⁸ , 1972	170 (37.6%)	RT + MD , Hb, PT, site, stage
McCombe & Jones ³¹ , 1993	357 (23.5%)	RT , ND, systemic disease, stage
Moses et al ³² , 1993	132 (21.%)	RT, postoperative feeding
Natvig et al ³³ , 1993	180 (11.7%)	RT , postoperative feeding, ND
Papazoglou et al ³⁴ , 1994	31 (9.0%)	RT , ND, systemic disease, site, stage
Robbins et al ³⁵ , 1972	23 (8.7%)	RT, ND, site, stage
Sarkar et al ³⁶ , 1990	110 (27.3%)	RT , ND
Sheman & Spiro ³⁷ , 1986	60 (11.7%)	RT, ND
Soylu et al ³⁸ , 1998	295 (12.5%)	Suture material , RT, ND, site, stage
Stell & Cooney ³⁹ , 1974	111 (15.3%)	RT
Thawley ⁴⁰ , 1981	155 (2.6%)	RT, site
Virtaniemi et al ¹² , 2001	133 (15.0%)	RT, Type of RT , ND, site, stage
Wei et al ⁴¹ , 1980	121 (22.3%)	RT , Hb, ND

Table 2: Relevant literature: fistula rates and potential aetiological factors described.

(RT, prior radiotherapy; ND, concurrent neck dissection; Hb, Low postoperative haemoglobin; PT, prior tracheostomy). **Bold** = interpreted as statistically significant.

Table 2 summarises much of the available literature regarding the incidence of PCF and influencing factors, including many of the studies reviewed by both Paydarfar and Cavalot and colleagues in their meta-analyses.^{3,16} Only studies relating specifically to total laryngectomy surgery were included. Apparent disparity between studies is evident in addition to variation in both fistula incidence and factors evaluated.

What Is The Role Of Reflux?

Gastroesophageal reflux disease is defined as the presence of reflux-related symptoms or oesophageal mucosal damage caused by the reflux of gastric contents. A diagnosis of GORD can often be made by analysis of the typical symptoms of heartburn and regurgitation.^{42,43} The incidence of GORD in the general population has been estimated to be in the range of 7-12%.⁴⁴ Multiple additional head and neck symptoms can be attributed to reflux, including globus sensation, hoarseness, halitosis, chronic cough, laryngospasm and throat discomfort.^{45,46} These atypical symptoms may occur in the absence of typical reflux sensations. 'Silent' GORD describes reflux without either typical or atypical reflux symptoms reported.

The question of the prevalence of silent reflux in the normal population has been examined and evaluated principally by 24-hour pH monitoring and/or endoscopy. Abnormal acid exposure was detected in up to 30% of healthy patients whilst a range of 10-15% of endoscopies demonstrated reflux-related macroscopic or microscopic pathology.⁴⁷

The extent of gastroesophageal reflux has been further examined and the term laryngopharyngeal reflux (LPR) introduced. Also known as gastropharyngeal reflux (GPR) or extraoesophageal reflux, this defines retrograde movement of gastric contents to the level of the pharynx and larynx. The effect of this gastric refluxate upon the upper aerodigestive tract mucosal lining was clarified by several early experimental studies. Severe mucosal erosion, ulceration and submucosal haemorrhages were recorded as a result of exposure to pepsin alone or to pepsin and hydrochloric acid in rabbit and cat models.^{48,49} Pepsin, a proteolytic digestive enzyme, was found to be the primary injurious component of the refluxate with greatest activity at

acidic pH levels. Experimental studies have also shown that intermittent reflux of only 3 episodes per week is sufficient to produce laryngeal damage when mucosal injury is present.⁵⁰

GORD has been suspected to be a potential aetiological factor for both inflammatory disease and malignancy of the upper aero-digestive tract, including the larynx. Whilst it has been estimated that the single greatest risk factor for squamous cell carcinoma (SCC) of the larynx is cigarette smoking, alcohol consumption is also associated with an increased risk and potentiates the risk when associated with smoking. Notably, smoking and alcohol consumption are also major risk factors for gastroesophageal reflux disease (GORD).⁵¹ The possible mechanisms of GORD carcinogenesis considered include chronic inflammation accompanied by the action of free radicals. Chronic inflammation results in a regular alternation of tissue damage and repair phases, known to have mutagenic potential. Free radicals produced by local neutrophils may cause cellular damage and necrosis.⁵²

A high incidence of GORD and GPR has been detected in patients with squamous cell carcinoma of the larynx in both pre- and post-laryngectomy populations. Ambulant 24-hour pH monitoring has been demonstrated to be the most reliable and accurate detection method of such reflux.^{53,54} When twenty-four patients with untreated laryngeal or pharyngeal squamous cell carcinoma were evaluated by ambulant 24-hour pH monitoring; only 4 of these 24 head and neck cancer patients were found to have neither laryngopharyngeal or gastroesophageal reflux.⁵⁵ A subsequent case-control study evaluating 22 patients with laryngeal SCC found an LPR rate of 63.9% compared to 20% in a control group ($P=0.03$).⁵⁶ Within a similar large case-control study, the multivariate analysis of Vaezi and colleagues also found GORD to be an independent risk factor for malignancy, although not to the same degree as smoking.⁵⁷

Gastroesophageal and gastropharyngeal reflux was monitored for the first 48 hours of the immediate postoperative period following laryngectomy by Garrido et al.⁵⁸ This pH-monitoring was conducted in 50 laryngectomy patients (40 total laryngectomies, 10 partial resections), detecting proximal reflux at the level of the pharyngeal closure in 40% of patients. In another

post-treatment study, GPR was detected by ambulant 24-hour pH monitoring in 9 of 11 asymptomatic laryngectomised patients.⁵⁹ Biacabe et al also conducted double-channel pH monitoring in 72 patients treated for pharyngolaryngeal carcinoma without symptoms of GORD; the incidence of silent reflux was approximately 37%.⁶⁰ It was therefore concluded that patients with advanced pharyngolaryngeal malignancy should be appropriately monitored and treated for acid reflux during their entire course of therapy.

The relationship between GORD and laryngeal carcinoma has, however, not yet been fully clarified and poses a significant epidemiological challenge. It has been recognised that a distinction between association and causality needs to be made whilst the matter is complicated by the relative rarity of carcinoma of the larynx when compared to the ubiquity of reflux.⁶¹ Existing case-control studies have been limited as controls need to be matched for lifestyle factors and there have been disparate study findings.⁶² Comparison of pH monitoring of 29 patients with carcinoma of the larynx with 2 groups of LPR patients, with and without benign laryngeal pathology did not detect a difference in the severity of reflux between the groups.⁶³ Reflux was therefore not found to be an independent risk factor although LPR was detected in 62% of the patients with malignancy.

A recent case-control study by Francis and colleagues attempted to explore this association further, matching 14,449 cases of laryngeal carcinoma with controls, sourced from the Veterans Health Administration dataset.⁶⁴ The resultant multivariate analysis did not reveal an association between GORD and laryngeal malignancy after adjustment for smoking and alcohol use. However further analysis did suggest a more specific link between GORD and glottic carcinoma whilst limitations relating to population bias and data consistency were acknowledged. This interpretation was mirrored by a large Swedish cohort study; no association was found after stratification for alcohol use was considered.⁶⁵ Qadeer's critical review concluded that the issue of causation remains unresolved; reflux may act as a co-carcinogen, possessing a synergistic role alongside smoking and alcohol to increase the risk of malignancy.⁶⁶

Over and above an increased prevalence of GORD in comparison to the general population, the treatment of head and neck cancer patients has been postulated to further increase the risk of reflux disease. Laryngectomy surgery results in changes of innervation of the pharyngeal plexus and in oesophageal motility. A decrease in sphincter contraction at the level of the proximal oesophageal segment accompanied by a pressure decrease at the level of the upper oesophageal sphincter has been observed, increasing the risk of reflux.^{67,68}

Whilst it is suspected that reflux may play a role in the aetiology of squamous cell cancer of the larynx, it has also been considered as a contributing factor to complications in head and neck cancer patients after surgery or during radiotherapy. The relationship between reflux and complications relating to the creation of a tracheoesophageal fistula (TOF) for post-laryngectomy speech rehabilitation has generated significant research interest. Bock et al evaluated the deposition of pepsin in TOF sites by tissue and fluid analysis in 17 laryngectomy patients finding pepsin in 12 subjects (58%). This appeared to be independent of the time from laryngectomy surgery and of reflux history.⁶⁹ Several studies have also suggested a correlation between pathological reflux and phonatory prosthesis problems such as granulation, increased frequency of prosthesis change and unsatisfactory vocal results.⁷⁰ In the vast majority of studies reflux was detected in a high proportion of patients with phonatory prosthesis problems. Comprehensive anti-reflux treatment has also resulted in a significant improvement in prosthesis-related dysfunction.⁷¹

Qadeer et al concluded that acid suppression therapy after treatment of laryngeal cancer (larynx-preserving surgery or chemo/radiotherapy) might have a protective effect in terms of recurrence.⁷² This was a retrospective case-control study in which a significant factor for decreased recurrence was acid suppressive therapy (hazard ratio 0.31 (95% confidence interval 0.13-0.75). It was reflected that there were several study weaknesses including reviewed bias and the classification of GORD; a prospective study would be required to better define this possible effect.

Antacid Treatment

A spectrum of treatment exists for GORD, the foundation being avoidance of aggravating factors. This prophylaxis comprises dietary and lifestyle modifications. A number of antacid medical treatments can supplement these adjustments. The first 'phase' of initial management includes the use of alginates and aluminium or magnesium containing antacids. These act to protect the oesophageal mucosa and are commonly used in response to symptoms. Histamine H₂ receptor antagonists such as ranitidine and cimetidine traditionally represent the second phase of medical treatment, suppressing acid secretion by selective inhibition of the parietal cell by histamine. As H₂ blockers do not inhibit other secretory pathways, total acid suppression is not achieved with these agents. Prokinetic drugs such as metocloperamide may also improve gastroesophageal sphincter function and gastric emptying.

The most recent class of GORD medical treatment introduced in 1989 is the group of proton pump inhibitors (PPIs) or 'hydrogen ion blockers'. These medications such as omeprazole and lansoprazole have been found to be the most potent suppressors of acid secretion, revolutionising the treatment of GORD.⁷³ They act by irreversibly binding to and inhibiting the H⁺,K⁺-ATPase enzyme of the gastric parietal cell. This inhibits both basal and stimulated acid secretion, whether stimulated by food, acetylcholine or by gastrin.⁷⁴ PPIs may be administered intravenously, orally and via a nasogastric feeding tube and have been proven to act within 24 hours to abolish acid secretion.⁷⁵ This rapid efficacy and potential for once-daily dosage has been found to increase compliance.⁵¹

Reflux Prophylaxis Following Total Laryngectomy

Antacid regimes in the postoperative period following total laryngectomy are employed by some surgeons with the aim of reducing the incidence of postoperative pharyngocutaneous fistulae. There is, however, a limited evidence-base to support such prophylaxis. Using the aforementioned search strategy, two single case-control studies with retrospective controls

were identified (Level 3B evidence) whilst no Level 1 nor Level 2 evidence was found.¹⁷

To date, medical literature describes the use of H₂ antagonists (such as cimetidine and ranitidine) as antacids. Seikaly and Park reported a significant decrease in the incidence of PCF with a postoperative regimen of intravenous ranitidine and the prokinetic, metocloperamide hydrochloride;⁷⁶ twenty-three cases were treated prospectively with the antacid regime (PCF incidence 0%) in comparison to 17 retrospective controls that did not receive antacid treatment (PCF incidence 26%). In this as yet small and specific research field this is a seminal study. It constituted a case-control study and did not benefit from randomisation. Although it is stated that the two groups were evenly matched for other factors of PCF risk, such as preoperative radiotherapy and disease factors, possible bias could have been introduced due to the lack of prospective controls. The antacid regime employed was two-fold (metocloperamide and ranitidine); a conclusion regarding the individual impact of each medication cannot be made. A further negative aspect of this regime is the use of prolonged intravenous medication (7 days). Of note, patients also received a week of intravenous antibiotics and an early feeding protocol was not used. The need for parenteral access for the first postoperative week could result in decreased patient mobility, and access site discomfort and sepsis. The associated cost of this regime of care is also a consideration.

A reduction in PCF incidence following the addition of a prokinetic medication to a postoperative antacid regime was also described in 2000.⁷⁷

Metocloperamide hydrochloride was added to a previous protocol of ranitidine. Of the group of 55 patients, a total of 32.1% developed fistulae; 39.4% in the ranitidine-only group and 21.7% in the ranitidine and metocloperamide group. As in Seikaly and Park's study, intravenous medications were used for the first postoperative week and a protocol of early postoperative feeding was not used. There are, however, several identifiable weaknesses with this study. It is neither prospective nor randomised. Matching of the two groups is also not described. A statistically significant difference between the two groups could not be concluded.

Published literature evaluating the perioperative use of PPIs was not identified. This represents a significant gap both in the existing literature and in evidenced-based practice. Use of PPIs would be of particular interest given the demonstrated increased efficacy and rapidity of action of this class of medications. Given the significant morbidity associated with PCF development, accompanied by increased hospital stay and healthcare costs it is imperative that risk factors for the development of such a complication be identified and controlled as far as possible. In the context of a postoperative early feeding protocol, exploration of the use of enteral medication is of interest.

To summarise, neither the use of a PPI nor the use of an enteral antacid preparation has been systematically examined; an exciting potential application of the PPI as reflux prophylaxis exists in the post-total laryngectomy setting. This generates an interesting research question. The ideal investigative study to determine whether a PPI would reduce the risk of PCF formation would be of prospective design using treatment and control groups. Randomisation into these 2 groups would reduce bias. 'Blinding' of the study would also increase its strength; a 'double-blind' format where neither patient nor healthcare professional is aware of the group of the patient is ideal. This is facilitated by use of a PPI placebo, identical in nature to the active drug so that neither clinician nor patient knows the true nature of the treatment received.

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PART C: PUBLICATION-READY MANUSCRIPT

THE EFFECT OF PERIOPERATIVE PROTON PUMP INHIBITORS ON THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULA FOLLOWING TOTAL LARYNGECTOMY: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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Keywords

Pharyngocutaneous fistula, laryngectomy, reflux, proton pump inhibitor, omeprazole

Format and style as dictated by the Author Guidelines, *Head & Neck* (Appendix VII)

STRUCTURED ABSTRACT

BACKGROUND:

Pharyngocutaneous fistula is a common complication of total laryngectomy. We hypothesized that perioperative proton pump inhibitor (PPI) treatment could reduce the incidence of pharyngocutaneous fistulae.

METHODS:

This prospective placebo-controlled double-blind randomized controlled trial compared PPI treatment (14 days enteral omeprazole) with a placebo in patients undergoing primary total laryngectomy. The incidence of pharyngocutaneous fistula was recorded.

RESULTS:

Forty patients were randomized into PPI (N = 21) and placebo arms (N = 19). One of 21 patients receiving omeprazole developed a fistula in comparison to 6 of 19 placebo group patients ($p=0.04$). No other statistically significant risk factors for pharyngocutaneous fistula were identified. The mean hospital stay of patients with and without a fistula was 32 and 7.5 days respectively.

CONCLUSIONS:

PPI prophylaxis was associated with a statistically significant reduction in pharyngocutaneous fistulae. As fistulae are associated with prolonged hospitalization and morbidity, PPIs are recommended for patients undergoing total laryngectomy.

INTRODUCTION

Pharyngocutaneous fistula is a common complication following primary total laryngectomy and is a cause of significant patient morbidity. The reported incidence of pharyngocutaneous fistula ranges from 3% to 65% with a reported average of 17.4%;¹ the incidence at our center has been previously evaluated and found to range between 15.4% and 20%.²

Development of a pharyngocutaneous fistula delays oral feeding and is associated with a significantly increased duration of hospital stay.

Bronchopneumonia, mediastinitis and severe sepsis, in addition to death as a result of erosion of the carotid artery have also been described.³⁻⁵ It is the principal short-term post-surgical complication to be avoided; all potential risk factors should be minimized.

Over 65 studies relating to risk factors for pharyngocutaneous fistulae after total laryngectomy have been reported, whilst the published literature extends over a period of 40 years.^{1,6,7} Multiple risk factors have been considered thus far and include systemic disease, low preoperative hemoglobin and perioperative blood transfusion, low postoperative albumin, preoperative tracheostomy, concurrent neck dissection, type of pharyngeal closure, postoperative vomiting, positive surgical margins, and the use of perioperative antibiotics.⁸⁻¹² Whilst there has been considerable disparity between studies, preoperative radiotherapy is thought to be the most significant factor identified to date.^{13,14}

A high incidence of gastroesophageal reflux disease (GERD) and gastropharyngeal reflux has been detected in patients with squamous cell carcinoma of the larynx in both pre- and post-laryngectomy populations.¹⁵⁻¹⁸ There is, however, little published literature concerning reflux prophylaxis in the perioperative laryngectomy setting. Seikaly and Park compared a protocol of intravenous ranitidine and metoclopramide against retrospective controls; it was suggested that this prophylactic regime decreased the incidence of pharyngocutaneous fistulae.¹⁹ A non-statistically significant

reduction in fistulae following the addition of metoclopramide to a postoperative antacid regime of ranitidine has also been described.²⁰

The most recent class of medication to be introduced in the spectrum of GERD treatment is the group of proton pump inhibitors (PPIs). These medications such as omeprazole and lansoprazole have been found to be the most potent suppressors of acid secretion, revolutionizing the treatment of GERD.²¹ They act by irreversibly binding to and inhibiting the H^+,K^+ -ATPase enzyme of the gastric parietal cell. PPIs may be administered intravenously, orally or via a nasogastric feeding tube and have been proven to abolish acid secretion within 24 hours.²² This rapid efficacy and potential for once-daily dosage has been found to increase compliance.²³ To our knowledge, neither the use of a PPI nor the use of an enteral antacid preparation has been systematically examined in the setting of total laryngectomy. This study was designed to evaluate the effect of this intervention on the incidence of pharyngocutaneous fistulae.

MATERIALS AND METHODS

Study population

All patients with advanced carcinoma of the larynx scheduled for primary total laryngectomy surgery at our institution over a 25-month period (1st January 2011 to 31st January 2013) were eligible for inclusion.

Study Design

A prospective placebo-controlled double-blind randomized controlled trial was conducted. Randomization was computer generated and both participants and clinical staff remained blinded to intervention groupings for the entire duration of the trial. Prospective data collection included patient demographics and known relevant risk factors for pharyngocutaneous fistulae.

All patients were managed according to an established 'early feeding' protocol.² Perioperative antibiotic care was standardized; a single dose of

intravenous cefazolin was given intraoperatively followed by 24 hours of intravenous antibiotics (ampicillin 1g tds and metronidazole 500mg tds). The total laryngectomy surgery and the postoperative care remained unchanged other than the addition of the PPI or placebo. The surgical method of closure of pharynx was also standardized. A 2-layer continuous closure with a vicryl 3/0 thread (Connell suture) in the shape of the least wound tension (either a horizontal or T-shaped closure) was performed by a consultant or a senior trainee under consultant supervision. A cricopharyngeal myotomy was routinely performed and a tracheoesophageal fistula created. Patients requiring a myocutaneous flap for augmentation of the pharynx were excluded.

A 20mg dose of omeprazole was administered once daily for 14 consecutive perioperative days, the first dose given the day before total laryngectomy surgery. All doses were given enterally, either per os or via a feeding tube using a MUPS (Multiple Unit Pellet System) preparation. Local prescribing guidelines, of both the manufacturer of the medication and of local pharmacology authorities were followed.²⁴

Statistical analysis

Proportions, mean and median values were calculated for all patient characteristics, as appropriate. The age distribution of the population was evaluated for normality with a Shapiro-Wilk test. Fisher's exact test (2-sided) was used to evaluate the primary outcome of pharyngocutaneous fistula development. Logistic regression analysis was also applied to assess the predictors of fistula development; the 'oddsrisk' routine was employed to convert the odds ratio into a risk ratio since generalized linear models to estimate the risk ratio did not converge. A two-tailed significance level of 0.05 was consistently used. Stata 11 software, StataCorp, College Station, Texas, USA was used to carry out all analyses.

The University of Cape Town Human Research Ethics Committee approved this study and all patients gave written informed consent.

RESULTS

A total of 40 patients (36 male and 4 female) underwent primary total laryngectomy at our institution during the 25-month study period and met our inclusion criteria. Mean patient age was 62.35 years (range 42-84 years); this was normally distributed.

Fifty-five percent of patients had a background of systemic disease whilst 12.5% had been previously treated for tuberculosis. A tracheostomy had been performed prior to total laryngectomy in 22 of the 40 patients (range 5-224 days). Concurrent neck dissection was performed in 39 of 40 patients; unilateral and bilateral neck dissections were undertaken in 16 and 23 patients respectively. A total of 62 neck dissections were performed (15 selective, 45 modified radical and 2 radical).

Pathological analysis revealed all tumors to be either T3 or T4 (7th edition American Joint Committee on Cancer (AJCC) staging system, 2009); 42.5% and 57.5% of patients had Stage 3 and 4 disease respectively. Metastatic neck disease was evident in 51.3% of the 39 patients who underwent neck dissection whilst nodal extracapsular spread was detected in 10 patients (25.6%).

After randomization, 19 patients received a perioperative placebo whilst 21 patients received PPI treatment. There were no statistically significant differences between patient and disease factors of the two groups (Table 1). None of the patients had previously been irradiated, had a prior diagnosis of GERD or was known to have received antacid treatment on a regular basis.

*Table 1: Placebo and PPI treatment group data**

Variable	Placebo (n=19)	PPI (n=21)
Mean age	63.5	61.3
Mean preop. haemoglobin (g/dl)	12.76	12.76
Mean preop. albumin (g/l) [‡]	37.15	38.90
Systemic disease	11 of 19 (57.9%)	11 of 21 (52.4%)
Prior tracheostomy (mean days)	32.4	38.0
Prior tracheostomy	10 of 19 (52.6%)	12 of 21 (57.1%)
Unilateral neck dissection	7	9
Bilateral neck dissection	12	11
Metastatic neck disease	7 of 19 (36.8%)	13 of 20 (65%)
Nodal extracapsular spread	4 of 19 (21.1%)	6 of 20 (30%)
Mean disease stage	3.53	3.62

Abbreviations: Preop, preoperative.

*No statistically significant difference between the two groups for any parameter ($p > 0.05$); [‡] Results available for 24 of 40 patients.

Seven patients (17.5%) developed a pharyngocutaneous fistula. A statistically significant difference was observed between the placebo and PPI treatment groups (Table 2). Spontaneous closure of the pharyngocutaneous fistula occurred in all cases (mean 32 days, median 30 days) and no related mortality was recorded. No adverse effects of the 14-day course of omeprazole treatment were noted.

Table 2: Incidence of pharyngocutaneous fistula

Outcome	Placebo	PPI	Total
Fistula	6 (31.6%)	1 (4.8%)*	7 (17.5%)
No fistula	13	20	33
Total	19	21	40

*Statistically significant (2-sided Fisher's exact test, $p = 0.04$)

Postoperative hospital stay was defined as the number of postoperative days until a patient was deemed fit for discharge from a surgical perspective. Table 3 demonstrates the differences seen between both placebo and treatment groups and between those with and without a pharyngocutaneous fistula.

Table 3: Comparison of postoperative stay

Average	Postoperative stay (days)			
	Placebo	PPI	Fistula	No fistula
Mean (SD)	14.95 (14.60)	9.19 (8.72)	32.00 (17.67)	7.52 (1.23)
Median (range)	8 (7-64)	7 (6-47)	34* (12-64)	7* (6-12)

*Statistically significant (Wilcoxon rank-sum test, $p = <0.001$)

The relative risk of other factors thought to influence pharyngocutaneous fistula risk is summarized in Table 4. A background of systemic disease was not found to be a statistically significant risk factor for pharyngocutaneous fistula development; the result is, however, suggestive of influence.

Table 4: Patient and disease/management factors: Evaluation of relative risk of pharyngocutaneous fistula

Variable		N	% Fistula development	Risk ratio (95% CI)
Systemic disease	No	18	5.6	4.9 (0.7 - 14.0)
	Yes	22	27.3	
Age	<60	18	16.7	1.1 (0.2 - 3.2)
	≥60	22	18.2	
Preoperative hemoglobin	<11.5	12	16.7	1.1 (0.2 - 3.4)
	≥11.5	28	17.9	
Metastatic neck disease	No	19	15.8	1.3 (0.3 - 3.6)
	Yes	20	20.0	
Prior tracheostomy	No	18	27.8	0.3 (0.1 - 1.3)
	Yes	22	9.1	
Unilateral ND	No	24	20.8	0.6 (0.1 - 2.2)
	Yes	16	12.5	
Bilateral ND	No	17	11.8	1.8 (0.4 - 5.2)
	Yes	23	21.7	
ECS	No	29	23.8	2.2 (0.5 - 5.1)
	Yes	10	30.0	
Margins <2mm or positive	No	6	16.7	1.1 (0.1 - 4.1)
	Yes	34	17.6	

Abbreviations: ECS, nodal extracapsular spread; ND, neck dissection.

DISCUSSION

The relationship between reflux and carcinoma of the larynx is an intriguing one; the debate surrounding association and causality is ongoing.²⁵⁻²⁷

It is clear, however, that patients with carcinoma of the larynx have a high prevalence of reflux. No patient in our study population had a prior diagnosis of GERD; the prevalence of GERD may be both underrepresented and undertreated in this group.

The treatment of these head and neck cancer patients has been postulated to further increase the risk of reflux. Laryngectomy results in changes in pharyngeal plexus innervation and in esophageal motility; a pressure decrease at the level of the upper esophageal sphincter has been observed.^{30,31} Reflux is also recognized as a key factor in phonatory prosthesis problems in the context of post-laryngectomy speech rehabilitation.^{28,29}

Evaluation of reflux by pH-monitoring for the first 48 hours of the immediate postoperative period following laryngectomy has also detected proximal reflux at the level of the pharyngeal closure in 40% of patients.³² The effect of this refluxate upon the upper aerodigestive tract mucosal lining has been examined; mucosal erosion, ulceration and submucosal hemorrhages were recorded as a result of exposure to pepsin or to pepsin and hydrochloric acid in animal models.^{33,34} Experimental studies have also shown that intermittent reflux of only 3 episodes per week is sufficient to produce laryngeal damage when mucosal injury is present.³⁵ This generates the hypothesis that reflux may contribute to poor wound healing and development of a pharyngocutaneous fistula.

The randomization of patients within this study resulted in matching of the placebo and treatment groups whilst the prospective double-blind design reduced the potential for introduction of bias. The overall incidence of pharyngocutaneous fistula was 17.5% and is comparable with reporting from other centers.¹⁰ The statistically significant difference between the proportion

of fistulae in the placebo and treatment groups supports the hypothesis that PPI reflux prophylaxis reduces the incidence of pharyngocutaneous fistulae.

Omeprazole is both widely available and inexpensive. The current pharmacy cost in our center of the treatment regime employed is 10.31 South African Rand/\$1.16 per patient. The medication is also easy to administer; lengthy parental administration is avoided and duplication in both first and third world settings is facilitated.

It is evident that our population presents with advanced disease. A prior tracheostomy was necessary in a large proportion of our patients. The wide-ranging interval between tracheostomy and total laryngectomy reflects several factors; delays in presentation to medical services and deviation from advised management plans often occur, coupled with pressure on surgical services.

CONCLUSIONS

Development of a pharyngocutaneous fistula is a common yet potentially devastating complication following total laryngectomy. It significantly increases hospital stay and cost, postpones oral intake, delays speech rehabilitation and can delay further treatment such as radiotherapy.

The use of perioperative enteral omeprazole is associated with a significant reduction in the incidence of pharyngocutaneous fistula in our setting. This strengthens the argument that postoperative reflux may contribute to pharyngocutaneous fistula formation. PPIs are recommended for patients undergoing total laryngectomy.

Acknowledgements

The authors thank the Groote Schuur Hospital pharmacy, Dr. Reddy's Laboratories Ltd, South Africa and Astra-Zeneca, South Africa for their facilitation of this study. No grants were received. No conflicts of interest to declare.

Word Count: 2175

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APPENDIX I: DATA COLLECTION

PATIENT FACTORS

- Hospital number
- Age
- Sex
- Smoking and alcohol intake history
- Diabetic / Non-diabetic
- Other major medical co-morbidity (COPD, CCF, HTN, liver disease)
- Nutritional status - albumin levels (pre/post-op)
- HIV status (and CD4 count)
- History of GORD prior to surgery
- Diabetic / Non-diabetic
- Haemoglobin levels (pre / post – op)
- ?Anaesthetic risk category

DISEASE-RELATED

- Previous radiotherapy & time interval between RT and surgery
- Previous tracheostomy

PROCEDURE-RELATED

- Suture material used
- Method of pharyngeal closure
- Myotomy performed
- Clearance of margins
- Nodal status – clinical stage and histologic grading
- Simultaneous neck dissection

POST-OPERATIVE FACTORS

- Local wound complications – haematoma, infection, breakdown
- Day of post-op feeding
- Drainage method and duration
- Post-op haemoglobin / blood transfusion required
- Post-operative vomiting

IN CASES OF PHARYGOCUTANEOUS FISULA

- Day post-op developed
- Site
- Spontaneous closure?
- Surgical closure? – method
- Day post-op closed

PHARYNGOCUTANEOUS FISTULA POST-TOTAL LARYNGECTOMY STUDY
Data sheet to be completed for all patients

Date of surgery:
 Name:
 Hospital number:

Age at surgery:

Sex: M / F

Smoking history: Current smoker / Ex – smoker / Lifetime non-smoker
 Cigs / day:

Alcohol use: Teetotal / Ex-drinker / Drinker
 (No. of units / week)

Diabetic: Y / N

Other major medical co-morbidity (COPD, CCF, HTN, liver disease)? Please give details:

Anaesthetic risk category: ASA I / II / III / IV

Haemoglobin: pre-op post-op

Albumin level: pre-op post-op

HIV status: + / - / refuses testing

CD4 count:

PMH of GORD Y / N / List current antacids:

Previous radiotherapy: Y / N
 - time interval between RT and surgery

Previous tracheostomy: Y / N
 - time interval between tracheostomy and surgery

Pre-op. staging: T____ N____

TOTAL LARYNGECTOMY SURGERY

Suture material used:

Method of pharyngeal closure:
 [Longitudinal / T – shape), Number of layers]

Myotomy performed: Y / N

Clearance of margins: Y / N

Nodal status – clinical stage and histologic grading: T____ N____

Simultaneous neck dissection: Y / N
 Unilateral / bilateral / selective / comprehensive

POST-OPERATIVE PERIOD

Local wound complications:
(haematoma, infection, breakdown)

Early feeding protocol used:

Y / N

Day post-op. started soft diet:

Day post-op. drain removed:

Blood transfusion required:

Y / N

Post-operative vomiting:

Y / N

Date declared fit for discharge from surgical perspective:
(excluding social and voice restoration issues)

IN CASES OF PHARYNGOCUTANEOUS FISTULA:

Day post-op developed:

Diagnostic criteria: Fever / Cellulitis / Clinical appearance of fistula / Contrast swallow

Site of PCF:

Left

Right

(Give details)

Day post-op fistula closed:

Spontaneous closure?

Surgical closure? (details)

Any queries, please contact Dr. Kate Stephenson, speed dial 76617

APPENDIX II: EARLY FEEDING PROTOCOL

Day	Feeding
0 (day of operation)	NBM + IV fluids
1	NBM + tube feeds
2	Clear fluids PO + 1500ml tube feeds
3	Free fluids PO + 1500ml tube feeds
4	Soft diet PO + 1500ml tube feeds
5	Full ward diet + 500ml feeds PO/NG
6 and onwards	As above

APPENDIX III: CONSENT FORM

CONSENT TO ACT AS A SUBJECT IN A CLINICAL STUDY

TITLE: DO PROTON PUMP INHIBITORS REDUCE THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULAE FOLLOWING TOTAL LARYNGECTOMY?

INVESTIGATORS: Dr Kate Stephenson and Professor Johan Fagan.

ADDRESS FOR ALL INVESTIGATORS: Division of Otolaryngology, H53, Old Main Building, Groote Schuur Hospital, Observatory, Cape Town, 7925

DESCRIPTION: You are being asked to participate in this study, which may necessitate the following:

Receiving an anti-acid medicine either by mouth or through a feeding tube to the stomach in the time after your laryngectomy (removal of the voice box) for cancer. Half of the patients in this study will receive this extra medicine and half will not; this will be decided randomly (i.e. by a method like flipping a coin).

RISKS AND BENEFITS: There are no known risks or benefits to you.

COSTS AND PAYMENTS: There will be no additional costs to you or your family.

CONFIDENTIALITY: The information obtained from this study will be published in the future such that your identity will remain anonymous. Medical records related to this study are confidential, but may be examined by researchers from this institution.

RIGHT TO WITHDRAW: You have the right to refuse to participate in this study at any time, and your decision will not adversely affect your care at this institution.

VOLUNTARY CONSENT: I understand what is stated above and agree to participate in this clinical trial.

Patient Name.....

Hosp No..... D.O.B:...../...../.....

Patient Signature.....

I certify that I have explained to the above individual the nature and purpose, the potential benefits, and possible risks associated with participating in this research study, have answered any questions that have been raised and have witnessed the above signature.

Witness / Researcher: Name.....

Signature.....

APPENDIX IV: HUMAN RESEARCH ETHICS COMMITTEE APPROVAL & UPDATES



UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

24 June 2010

HREC REF: 186/2010

Dr K Stephenson
Otolaryngology
H53, Old Main Building

Dear Dr Stephenson

PROJECT TITLE: DO PROTON PUMP INHIBITORS REDUCE THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULAE FOLLOWING TOTAL LARYNGECTOMY?

Thank you for responding to the issues raised by the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Please add the HREC contact details on the Informed Consent Document.

Approval is granted for one year till the 30th June 2011.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

S Thomas

Annual Progress Report

Date	10 TH May 2011
HREC REF Number	186/2010
Protocol number (if applicable) & Protocol title	DO PROTON PUMP INHIBITORS REDUCE THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULAE FOLLOWING TOTAL LARYNGECTOMY?
Principal Investigator	Dr. Kate Stephenson
Department / Office Internal Mail Address	Department of Otorhinolaryngology, H-53, Old Main Building, Groote Schuur Hospital

List of documentation

N / A



HREC office use only (FWA00001637; IRB00001938)			
Approved <input checked="" type="checkbox"/>	This serves as notification of annual approval, including all documentation described above.		
Not approved	See attached comments.		
Type of review	Expedited <input checked="" type="checkbox"/>	Full committee	
Expiry date	15 JUNE 2012		
Signature	Signed by candidate		Date
Chairperson of the HREC			6.6.11



Annual Progress Report

Date	21 th Sept 2012
HREC REF Number	186/2010
Protocol number (if applicable) & Protocol title	DO PROTON PUMP INHIBITORS REDUCE THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULAE FOLLOWING TOTAL LARYNGECTOMY?
Principal Investigator	Dr. Kate Stephenson
Department / Office Internal Mail Address	Department of Otorhinolaryngology, H-53, Old Main Building, Groote Schuur Hospital

List of documentation

N / A

RESEARCH ETHICS COMMITTEE

2012 -09- 28

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

HREC office use only (FWA00001637; IRB00001938)

<input checked="" type="checkbox"/> Approved	This serves as notification of annual approval, including all documentation described above.		
<input type="checkbox"/> Not approved	See attached comments.		
Type of review	<input checked="" type="checkbox"/> Expedited	<input type="checkbox"/> Full committee	
Expiry date	15 SEPTEMBER 2013		
Signature		Date	
Chairperson of the HREC	PP TUBurgess		05/10/2012

APPENDIX V: DEPARTMENTAL RESEARCH ETHICS COMMITTEE APPROVAL



UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee

Professor Anwar Suleman Mall
J-45 Room Old Main Building, Groote Schuur Hospital,
Observatory 7925, South Africa
Tel (021) 406 6168/6232/6227 Fax (021) 448 6461
Email: Anwar.Mall@uct.ac.za

23rd April 2010

Dr K Stephenson
Department of Surgery
Division of Otolaryngology
Groote Schuur Hospital
University of Cape Town

Dear Dr Stephenson

RE: PROJECT 2010/025

PROJECT TITLE: Do proton pump inhibitors reduce the incidence of pharyngocutaneous fistulae following total laryngectomy

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

Signed by candidate

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE

"OUR MISSION is to be an outstanding teaching and research university,
educating for life and addressing the challenges facing our society."

APPENDIX VI: SOUTH AFRICAN NATIONAL HUMAN RESEARCH COMMITTEE TRIAL REGISTRATION



TRIAL APPLICATION

Application ID:	2244	DOH Number	Pending	Page:	1/2
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Applicant Details

Organisation : UCT Department of Otolaryngology
 Applicant Type : Academic Investigator
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 Fax : 0214488805
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 Responsible Contact person
 (for public) Prof. J J Fagan
 Telephone : 0214068420
 Research contact person Dr. Kate Stephenson
 Telephone : 0798162044

Trial Application Details

Issue Date : 2010/04/25
 Sponsors : A research grant will be applied for from the ENT Society once Ethics Approval is obtained.
 The omeprazole for the trial needs to be purchased. Dr. Reddy Pharmaceuticals may provide omeprazole capsules needed for the trial free of charge - this is to be
 Primary Sponsor : N/A
 Funding Type : Requires Funds to be Raised
 Research Site Names : Groote Schuur Hospital, Cape Town
 Primary Research Site Name :
 Total National Budget for Trial : R 15000 (less than)
 Protocol / Grant Reference Number 0-1253

TRIAL APPLICATION

Application ID: 2244	DOH Number	Pending	Page: 2/2
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	Study Descriptive Information
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Brief Title of Study .

Full Title of Study : DO PROTON PUMP INHIBITORS REDUCE THE INCIDENCE OF PHARYNGOCUTANEOUS FISTULAE FOLLOWING TOTAL LARYNGECTOMY?

Anticipated Start Date : 2010/07/01

Anticipated End Date : 2012/07/01

Target Sample Size : 100

Study Phase : Phase 4

Study Scope :

Study Type :
Interventional

Disease Type Heading : Ear, Nose and Throat Diseases

Disease Type Condition :

Intervention Name (General)

Intervention Name (General):	No	Yes
Intervention Duration:	No	Yes

THE UNIVERSITY OF CHICAGO

AN

Interventional

Intervention Type : Registered Drug

Purpose :

Allocation : Randomised

Masking : Double Blind

Control:

Parallel Assignment -

Endpoints:

Environpoints	Efficacy
1	0.00
2	0.00
3	0.00
4	0.00
5	0.00
6	0.00
7	0.00
8	0.00
9	0.00
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96	0.00
97	0.00
98	0.00
99	0.00
100	0.00

Study Descriptive Information

Recruitment Status as at Date: 2010/04/25

Recruitment Status : Not Yet Recruiting

Gender : Both

Ethnicity : All

Age: From Years To Years

Qualifying Disease Condition
Squamous cell carcinoma of the larynx undergoing total

for Inclusion : laryngectomy

Major Exclusion Criteria:

Severe liver disease

Key Primary Outcome : Incidence of pharyng

Key Secondary Outcomes : Duration of post-operative hospital stay

from a surgical perspective

APPENDIX VII: AUTHOR GUIDELINES: HEAD & NECK

Edited By: Ehab Y. Hanna, MD

Impact Factor: 2.403

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46/199 (Surgery)

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Numbers. Use numerals for all units of measure and time. Spell out the numbers one through nine only for general usage (eg, "We considered only two possibilities.") Spell out numbers beginning a sentence.

Abbreviations. Use only standard abbreviations. Avoid abbreviations in the title. The full term for which an abbreviation stands should precede its first mention in the text. Only standard abbreviations as listed in the *AMA Manual of Style* should be used without definition.

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Title Page. The title page should include (1) a concise and informative title of the article using terms that can be readily indexed; (2) the authors' full names (first name, middle initial, surname) with highest earned degrees; (3) affiliations for each author (department, section, institution, city and state or country where the work was done); (4) acknowledgment of grant support and of individuals who were of direct help in the preparation of the study; (5) identification of meetings at which the manuscript was presented, if appropriate; (6) the name, address, telephone number, and email address of the author to whom correspondence and/or reprint requests are to be sent; (7) a brief running title; and (8) five key words for indexing.

Authorship. All persons designated as authors should have participated sufficiently in the work to take public responsibility for the content of the manuscript. Authorship credit should be based on substantial contributions to (1) conception and design or analysis and interpretation of data, (2) drafting

of the manuscript or revising it for important intellectual content and, (3) final approval of the version to be published. The Editor may require the authors to justify assignment of authorship. In the case of collective authorship, the key persons responsible for the article should be identified and others contributing to the work should be recognized with proper acknowledgment.

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Present your results in logical sequence in text, tables, and figures. Avoid duplication of data in the text and tables, figures, or both. Emphasize or summarize only important observations. In a discussion, emphasize new and important aspects of the study and the conclusions that follow from them. Avoid repetition and present recommendations. If case reports are necessary to illustrate a point, they should contain only the pertinent information.

All tables and figures should be numbered consecutively at first mention in the text. All data cited in the text should be checked carefully against data in the tables to be sure they correspond. All names cited in the text should be checked carefully against the references to ensure the spelling is correct.

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legend should be numbered in accordance with a sequence established by the first mention in the text of the particular table or figure. *Head & Neck* follows the Uniform Requirements for reference style:

Journal article (list all authors when six or less; when seven or more, list only first three and et al.)

King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. *J Comp Neurol* 1998;390:537-551.

Book

Voet D, Voet JG. *Biochemistry*. New York: John Wiley & Sons; 1990. 1223 p.

Book chapter

Gilmor ML, Rouse ST, Heilman CJ, Nash NR, Levey AI. Receptor fusion proteins and analysis. In: Ariano MA, editor. *Receptor localization*. New York: Wiley-Liss; 1998. p 75-90.

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APPENDIX VIII: POST-STUDY EVALUATION

Sample Size

From statistical power calculations it was initially anticipated that 50 patients would be recruited into each arm of the study, with an estimated trial duration of 2 years. In the 25-month study period, a total of 40 patients were eligible for inclusion within the analysis. Several factors affecting patient numbers can be identified. Firstly, the trial start date was later than hoped due to delay in availability of medicines and subsequent necessary detailed planning with the hospital pharmacy. Patient numbers were also reduced by adherence to strict inclusion criteria; cases requiring extended surgery such as loco-regional flaps were excluded in addition to those who were not managed according to an early feeding protocol, as described. Cases in which the medicine was not administered as intended were also excluded. The termination point of the study was dictated by the expiry date of the available medications used specifically for purposes of the trial.

Amendments to the protocol were not required and there were no deviations from the protocol in those cases considered eligible for inclusion within the study.

Future research

Several areas of further research related to this work can be identified. Additional experimental studies may serve to better characterise and quantify the damaging effect of refluxate upon the pharyngeal mucosa. A better understanding of the degree and nature of reflux in both pre- and post-

laryngectomy populations would also support possible interventions. This could be approached in several ways; reported symptoms, pH monitoring, endoscopy and combined pH-impedance monitoring are possible methods of evaluation.

Similar trials, ideally also of double-blind, placebo-controlled design could also be compared to this work and facilitate a meta-analysis. Larger patient numbers might be achieved with a multi-centre set-up. Variations in the dosage and mode of administration of the proton pump inhibitor (intravenous versus enteral) would also be avenues of exploration, in addition to use of other medicines within the same class or combinations of antacids.

Comparative continuous (24 hours or greater) pH monitoring in the perioperative period would be an ideal tool for evaluation of the reflux pattern and impact of the proton pump inhibitor.

Examination of the use of omeprazole in the perioperative care of 'salvage laryngectomies', after radiotherapy or chemoradiotherapy would also be of interest, particularly as the risk of pharyngocutaneous fistula is recognised to be higher in these circumstances.

This work suggests that there is significant potential for reduction of pharyngocutaneous fistulae and improved patient outcomes. High quality research is required to definitively answer the question of the impact of reflux on risk of developing pharyngocutaneous fistulae after total laryngectomy. Numerous additional patient, disease and management-related potential risk factors may confound the issue, necessitating extensive data collection and evaluation.

APPENDIX IX: LIST OF CORRECTIONS

1. Spelling: correction of counseled to counselled (p.16)
2. Addition of Appendix VIII: Post-study evaluation

University of Cape Town